CHRONIC TOXICITY SUMMARY

SILICA (CRYSTALLINE, RESPIRABLE)

(silicon dioxide, quartz, tridymite, cristobalite)

CAS Registry Number: 7631-86-9

I. Chronic Toxicity Summary

Inhalation Reference Exposure Level	**3 µg/m^3 (respirable; MMAD ≤ 10 µm)**
Critical effect(s)	Silicosis in miners and other workers
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 2001)

Description	Transparent crystals
Molecular formula	SiO_2
Molecular weight	60.09 g/mol
Density	2.65 g/cm^3 @ 0 °C (quartz)
Melting point	1610 °C
Boiling point	2230 °C (2503.20 °K)
Vapor pressure	10 torr @ 1732 °C
Solubility	Practically insoluble in water or acids, except hydrofluoric acid; very slightly sol. in alkali.
Conversion factor	Not applicable

In crystalline silica, the silicon and oxygen atoms are arranged in a definite regular pattern throughout the crystal. The characteristic crystal faces of a crystalline form of silica are the outward expression of this regular arrangement of the atoms (HSDB, 2001). This REL is meant to be applied only to respirable, crystalline silica (quartz, cristobalite, tridymite), that is, to that fraction less than or equal to 10 µm mass mean aerodynamic diameter (MMAD).

III. Major Uses and Sources

At least 11 chemically identical forms (polymorphs) have been described for crystalline silica. Alpha-quartz is the most abundant polymorph and constitutes 12% of the earth's crust (Elzea, 1997). Silica is also found in the amorphous (non-crystalline) state. The amorphous silica in diatomaceous earth (composed mainly of the cell walls of diatoms) can be converted to the crystalline form cristobalite by heating to 1000-1100 ºC (calcining).

The major uses of silica are in the manufacture of glass, of abrasives, ceramics, and enamels, in scouring and grinding compounds, and in molds for castings. Silica is also used in decolorizing and purifying oils and petroleum products; as a clarifying agent; in filtering liquids; and in the manufacture of heat insulators, firebrick, and fire- and acid-proof packing materials. As diatomite (naturally occurring diatomaceous earth), silica is used as a filtration agent, as an

abrasive, and as an industrial filler. Sources of respirable crystalline silica in California include mines, quarries, diatomaceous earth calcining plants, and entrained fines (e.g., PM_{10}) from surface soil. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 2,537,500 pounds of crystalline silica (CARB, 1999).

IV. Effects of Human Exposures

Inhalation of crystalline silica initially causes respiratory irritation and an inflammatory reaction in the lungs (e.g., Vallyathan *et al*., 1995). Acute exposures to high concentrations cause cough, shortness of breath, and lipoproteinosis of the lung. After chronic workplace exposures to silica for six to sixteen years, the small airways become obstructed as measured by pulmonary function tests (e.g., decreased FEV_1) in granite quarry workers (no measurement of silica levels reported; Chia *et al*., 1992). In a report on the hazards of exposure to crystalline silica, the American Thoracic Society (1997) stated: "Studies from many different work environments suggest that exposure to working environments contaminated by silica at dust levels that appear not to cause roentgenographically visible simple silicosis can cause chronic airflow limitation and/or mucus hypersecretion and/or pathologic emphysema"

Silicosis results from chronic exposure and is characterized by the presence of histologically unique silicotic nodules and by fibrotic scarring of the lung. The histological progression of silicosis has been described as: (1) granuloma composed of histiocytic cells, collagen, and lymphocytes; (2) cellular fibrotic nodule with irregular collagen at the center and circular collagen at the periphery; (3) more mature nodule with acellular and avascular center; and (4) late mature nodule composed of dust and collagen including a calcified center (Green and Vallyathan, 1996).

The initial diagnosis of silicosis is often by chest radiographs. Recent papers have used the 1980 classification by the International Labor Organization (ILO, 1980) to identify and classify silicosis into categories and subcategories of seriousness by comparison of patient radiographs with ILO-supplied radiographs taken at various stages of silicosis:

ILO Category	*Qualitative Description*
0/0	No small (up to 1 cm) silicotic opacities (nodules) are present
0/1	Probably no nodules, but some areas of radiograph are suspect
1/0	Small silicotic nodules are most likely present, but not certainly
1/1	Small silicotic nodules are definitely present
1/2	Small silicotic nodules are definitely present; other areas of the radiograph may indicate more advanced lesions including large opacities (> 1 cm), pleural thickening, etc.
2/1, 2/2, 2/3, 3/2, 3/3	More advanced stages of silicosis/increasing certainty of the presence of lung abnormalities

Some reports (e.g., Kreiss and Zhen, 1996; Hughes *et al*., 1998) use 1/0 as the basis of classification of silicosis, since many cases of silicosis are not detected by chest radiographs, yet silicotic nodules and other lesions are found at autopsy (Craighead and Vallayathan, 1980;

Hnizdo *et al*., 1993). Other reports (e.g., Hnizdo and Sluis-Cremer, 1993) use the definite 1/1 as the lowest category indicating silicosis. Some disease is missed by radiography and is determined only by autopsy (Hnizdo *et al*., 1993).

A. Environmental silicosis

Several studies have reported "environmental silicosis", cases where the silicosis occurs in the absence of an industry usually associated with the disease (reviewed by USEPA, 1996). In one of the stronger examples, Saiyed *et al*. (1991) investigated non-occupational pneumoconiosis in Ladakh, India, high in the western Himalayas where there are no mines or industries. Among 449 randomly selected inhabitants of three villages there were many cases of pneumoconiosis associated with progressive massive fibrosis (nodules > 1 cm) and "egg shell" calcification of hilar glands. The prevalence of pneumoconiosis was 2.0% (3/150) in the village of Saboo, 20.1% (31/149) in Shey, and 45.3% (68/150) in Chushot, and corresponded with the severity of dust storms and the presence or absence of chimneys in the kitchens (i.e., ventilated cooking). Without chimneys (Chushot), dust concentrations in kitchens averaged 7.5 mg/m^3 during cooking periods. The free silica content of the dust storms was 60-70%. The authors suggested that exposure to free silica from dust storms and to soot from cooking with domestic fuels caused the pneumoconiosis. Perhaps the interaction of silica and soot led to the disease. Such exposures in this and other studies, such as Bar-Ziv and Goldberg (1974), might be considered to be non-industrial but occupational since the subjects studied by Saiyed *et al*. (1991) were involved in the domestic work of cleaning and cooking (USEPA, 1996). In any case the exposures were very high and thus similar to some occupational exposures.

B. Occupational silicosis

Several relatively recent reports have presented data that allow a quantitative relationship between occupational dust exposure and the development of silicosis in workers to be calculated.

<u>Hard rock miners in Ontario, Canada (Muir *et al*., 1989)</u>

Muir *et al*. (1989) examined the relationship between cumulative exposure to silica (free crystalline silica, specifically alpha-quartz) and the development of silicosis in 2109 male hard rock (uranium, gold, mixed metals) miners in Ontario, Canada. The miners began work between 1940 and 1959 and were followed either until they ended their dust exposure or until December 31, 1982 (whichever came first). Five X-ray readers examined chest radiographs; one or more readers identified 32 cases of silicosis, defined as ILO category 1/1 or greater with round opacities. All five readers agreed on only six cases, while 12 cases were identified by only one reader (Table 1). A Weibull model of the form

$$R(x) = 1 - \exp[-(\alpha x)^{\beta}] \quad (x \geq 0, \beta > 0)$$

gave the best fit to the data for cumulative risk R of silicosis as a function of cumulative exposure in units of (mg/m^3)-yr. In this model x is the cumulative exposure (lagged five years), α is the Weibull scale parameter, and β is the Weibull shape parameter (Table 1). Estimates of α and β for each reader are given in Table II of Muir *et al*. (1989).

Table 1. Silicosis Risk *vs.* Cumulative Respirable Silica in (mg/m^3)-y (Table IV of Muir et al.)

Reader	*Cases (n)*	*1% risk* [a]	*2% risk*	*5% risk*	*10% risk*
1	14	3.5 (2.4-5.1)	5.7 (3.9-8.4)	11.2 (6.8-18.2)	18.6 (9.9-35.0)
2	24	2.7 (2.0-3.6)	4.1 (3.2-5.3)	7.1 (5.5-9.1)	10.9 (8.1-14.8)
3	24	3.0 (2.3-3.9)	4.3 (3.4-5.3)	6.9 (5.6-8.5)	9.9 (7.8-12.7)
4	14	3.7 (2.6-5.2)	5.6 (4.1-7.7)	9.8 (6.7-14.3)	15.1 (9.3-24.4)
5	7	5.7 (4.0-8.0)	7.8 (5.5-11.0)	11.9 (7.8-18.3)	16.5 (9.7-28.2)
Any reader	32	2.1 (1.6-2.9)	3.3 (2.6-4.2)	6.0 (4.8-7.5)	9.6 (7.3-12.5)
At least 3	15	3.5 (2.5-4.9)	5.4 (4.0-7.3)	9.5 (6.6-13.6)	14.6 (9.3-23.2)
All readers	6	6.1 (4.1-8.9)	8.5 (5.6-12.8)	13.2 (7.8-22.5)	18.7 (9.7-36.1)

[a] In parentheses is the 95% confidence interval (CI) for each risk estimate.

The Ontario cohort gives the shallowest dose-response relationship for silicosis of the several cohorts examined (see Summary Table 13 below) due in part to the lack of follow-up of members who left the mines (either for another type of work or for retirement). Silicosis often develops after leaving employment (Hnizdo and Sluis-Cremer, 1993; Chen *et al*., 2001). In Hnizdo and Sluis-Cremer (1993), for more than half the cases of silicosis radiographic signs developed at an average of 7.4 years after mining exposure ended. In addition, some of the Ontario miners in the Muir *et al*. study may have changed to a less dusty job if their physician told them that their (annual) radiograph showed abnormalities. The lack of follow-up, leading to under-ascertainment of silicosis, is a serious limitation of this study.

Gray iron foundry workers (Rosenman *et al*., 1996)

Rosenman *et al*. (1996) evaluated 1,072 (96.8% males) current and retired workers in a Mid-western gray iron foundry, which produces engine blocks for the automotive industry. Medical records and silica exposure data were analyzed for those with at least 5 years of employment as of June 1991. Nearly half had worked at the foundry for 20 years. Sixty had radiographic evidence of pneumoconiosis (ILO categories 1/0 and greater). Twenty-eight workers had radiographs consistent with silicosis; of these 25 had simple silicosis and three had progressive massive fibrosis. The prevalence of radiographic changes consistent with silicosis increased with years at the foundry, work area, quantitative silica exposure, and cigarette smoking. In regard to quantitative silica exposure, the authors stated that 0.3-2.7% of workers at the OSHA standard (90-100 μg/m^3) were silicotic, as were 4.9-9.9% of workers above 100 μg/m^3. After controlling for confounders, Rosenman *et al*. (1996) used a logistic regression analysis based on cumulative silica exposure to determine an odds ratio of 1.45 for developing a radiograph consistent with silicosis after 20 years of work at 100 μg/m^3 and an odds ratio of 2.10 after 40 years of work at 100 μg/m^3 (Tables 2 and 3). This study probably underestimates risk due to lack of follow-up of the current workers. Although silica is not the only chemical in a foundry, the unique nature of the silicotic nodule diminishes the likelihood of confounding by other exposures.

Table 2. Silicosis risk based on Rosenman *et al*. data (Finkelstein, 2000)

Cumulative silica exposure	*Prevalence of silicosis*
< 2 (mg/m^3)-y	0.4%
2-6 (mg/m^3)-y	2.7%
> 6 (mg/m^3)-y	10%

Table 3. Odds ratios for silicosis (from Table 8 of Rosenman *et al*.)[a]

Time-weighted Average Silica Exposure (mg/m^3)	*20-year Cumulative Exposure [(mg/m^3)-y]*	*Odds ratio (95% C.I.)*	*40-year Cumulative Exposure [(mg/m^3)-y]*	*Odds ratio (95% C.I.)*
0.010	0.2	1.04 (1.02-1.15)	0.4	1.08 (1.05-1.11)
0.025	0.5	1.10 (1.06-1.14)	1.0	1.20 (1.12-1.30)
0.050	1.0	1.20 (1.12-1.30)	2.0	1.45 (1.25-1.68)
0.075	1.5	1.32 (1.18-1.47)	3.0	1.74 (1.40-2.17)
0.100	2.0	1.45 (1.25-1.68)	4.0	2.10 (1.15-2.82)
0.150	3.0	1.74 (1.40-2.17)	6.0	3.04 (1.96-4.72)
0.200	4.0	2.10 (1.56-2.82)	8.0	4.40 (2.45-7.93)
0.300	6.0	3.04 (1.96-4.72)	12.0	9.24 (3.83-22.3)

[a] Additional mean silica exposures, their calculated odds ratios, and 95% confidence intervals (C.I.) are given in the paper.

Diatomaceous earth workers in California (Hughes *et al.,* 1998; Park *et al*., 2002)

Hughes *et al.* (1998) investigated 1,809 Caucasian male diatomaceous earth workers in Lompoc, California, who had at least one year of exposure to cristobalite between 1942 and 1987. In nature, diatomaceous earth contains amorphous silica (composed mainly of the cell walls of diatoms). Heating diatomaceous earth to a high temperature (calcining; 1000-1100 °C) causes the crystalline silica isomorph cristobalite to form. Quantitative estimates of dust exposure were made and published in the peer-reviewed literature by Seixas *et al*. (1997) based on 6395 air sampling records taken from 1948-1988. The average estimated respirable dust concentrations for 135 jobs were 3.55 ± 1.25 mg/m^3 prior to 1949, 1.37 ± 0.48 mg/m^3 from 1949-1953, 0.47 ± 0.16 mg/m^3 from 1954-1973, and 0.29 ± 0.10 mg/m^3 from 1974-1988. The workers had periodic chest radiographs. Based on the median of radiographic readings by three independent readers, 81 workers (4.5%) were judged to have opacities on chest radiographs (small opacities, ILO profusion ≥ 1/0, and/or large opacities). Age-adjusted relative risk of opacities increased significantly with cumulative exposure to crystalline silica. The concentration of respirable crystalline silica was an important determinant of risk after accounting for cumulative exposure. The workers were split into two categories: those exposed to < 0.50 mg/m^3 (or hired after 1950) and those exposed to > 0.50 mg/m^3 (or hired before 1950). The risk of opacities for a cumulative exposure to crystalline silica of 2.0 mg/m^3-yr is shown in Table 4.

Table 4. Silica exposure and silicosis based on data of Hughes *et al.* (1998)

Average crystalline silica exposure	*Cumulative risk of silicotic opacities*
< 0.50 mg/m^3 (or hired after 1950)	1.1%
> 0.50 mg/m^3 (or hired before 1950)	3.7%

The findings of Hughes *et al.* (1998) indicate an exposure-response relationship between cumulative exposure to crystalline silica as cristobalite and radiographic opacities. The relationship was substantially steeper among those exposed at the highest average concentrations of crystalline silica. The authors believe that the data do not support the regulatory assumption that cristobalite is more fibrogenic than quartz (i.e., prior to 2000 the occupational limit for cristobalite was half that for quartz), since at average silica levels comparable to other epidemiologic studies quartz gave a higher incidence of silicosis than did cristobalite in this study. However, since radiography can under-diagnose silicosis, complete accounting for silicosis will require evaluation at autopsy. The ACGIH recently lowered the TLV for alpha-quartz from 100 to 50 μg/m^3, so that it has the same TLV as cristobalite.

Park *et al*. (2002) carried out a quantitative risk assessment, by Poisson regression methods, of lung disease other than cancer (LDOC) (largely silicosis and excluding pneumonia) occurring among the diatomaceous earth workers in Lompoc. A linear relative risk model gave the best fit to the data. They estimated an excess lifetime risk for radiographic silicosis of 68-75 cases per thousand workers exposed to 50 μg/m^3 silica (cristobalite) for a 45 year work-life, then living to age 85. At 1 μg/m^3 silica the excess lifetime risk was estimated to be 1.6 cases of lung disease other than cancer per thousand workers exposed (Table 5).

Table 5. Excess lifetime risk of silicosis predicted by Park *et al.* (2002)

Concentration (mg/m^3)	*45 year cumulative exposure in mg/m^3-y*	*Radiographic silicosis - all workers*	*Radiographic silicosis in workers with < 10 mg/m^3-y*
0.001	0.045	6.2/1000*	1.6/1000
0.005	0.225	17/1000	7.8/1000
0.01	0.45	26/1000	16/1000
0.02	1.8	39/1000	31/1000
0.05	2.25	68/1000	75/1000
0.1	4.5	100/1000	140/1000
0.2	9	150/1000	260/1000

* Excess risk estimates assume that workers were exposed to a constant silica concentration for up to 45 years (ages 20-65). Annual risks are accumulated up to age 85.

South African gold miners (Hnizdo and Sluis-Cremer, 1993)

Hnizdo and Sluis-Cremer (1993) investigated silicosis risk retrospectively in a cohort of 2,235 white male South African gold miners. Exposure estimates were made for nine separate occupational categories based on a special study of dust levels in these mines done by Beadle in the 1960s (Beadle, 1971). The workers had a minimum of 10 years and an average of 24 years service from 1940 until the early 1970s. The miners had an annual chest radiograph while mining, and were followed until 1991 for radiographic signs of the onset of silicosis. An ILO

category 1/1 or greater was selected to designate silicosis. Two independent readers initially read the chest films, but only the reader whose interpretations correlated better with autopsy results was used for additional analysis; the use of one reader is a limitation of the study. There were 313 miners (14% of the cohort) who developed radiographic signs of silicosis at an average age of 55.9 years. The latency period was largely independent of the cumulative dust exposure (CDE). In 57% of the silicotics, the radiographic signs developed at an average of 7.4 years after mining exposure ceased. The risk of silicosis determined by chest radiographs increased exponentially with cumulative dust dose. At the highest level of 15-(mg/m^3)-years CDE (approximately 37 years of gold mining at an average respirable dust concentration of 0.4 mg/m^3), the cumulative risk for silicosis reached 77% as estimated by the accelerated failure time model using the log-logistic distribution (SAS Proc LIFEREG):

$$CR(t) = 1 - \{1/[1 + \exp(-\mu/\sigma) \times t^{(1/\sigma)}]\}$$

where CR(t) = cumulative risk at time t, and μ (2.439) is the intercept and σ (0.2199) is the scale parameter estimated by SAS's LIFEREG procedure. The authors concluded that the risk of silicosis was strongly dose-dependent, but that the latency period was largely independent of dose. The life table analysis (SAS Proc LIFETEST) below (Table 6) shows the number of miners who developed silicosis ("cases"), the number of miners considered by the authors to be at risk, and the risk per unit of CDE (also as calculated by the authors). In the table in column 1 (in parentheses) are OEHHA's determination of the mg/m^3–yr respirable silica exposure, based on Hnizdo and Sluis-Cremer's estimate of 30% silica in the dust, and in column 4 is the total number of miners actually at each midpoint level of CDE or silica.

Table 6. Life table results - Risk of silicosis per unit Cumulative Dust Exposure (CDE)
(from Table IV of Hnizdo and Sluis-Cremer, 1993)

Midpoint in (mg/m^3)-y of CDE (silica)	*Cases of silicosis*	*Number of workers at risk*	*Number of workers at this CDE midpoint*	*"Risk/ unit CDE"*	*Mean years in dust*	*Mean dust conc. (mg/m^3)*
1 (0.3)	0	2218	204			
3 (0.9)	9	2014	474	0.002	20.5	0.17
5 (1.5)	48	1540	556	0.016	23.5	0.24
7 (2.1)	85	984	469	0.045	27.2	0.30
9 (2.7)	93	515	318	0.099	28.0	0.33
11 (3.3)	53	197	142	0.156	29.4	0.38
13 (3.9)	20	55	44	0.222	31.5	0.41
15 (4.5)	5	11	11	0.227	37.0	0.42

[a] CDE = Σ number of dusty shifts x mean mass respirable dust conc. x average number of hours spent underground / (270 shifts x 8 h/shift)

A plot of risk of silicosis per unit of Cumulative Dust Exposure (CDE) versus the mid-point unit CDE, as given in Figure 1 of the Hnizdo and Sluis-Cremer report, and a plot of % silicosis among the workers actually exposed to a given level of silica (Figure 2), as determined by OEHHA staff, respectively, are given below.

Figure 1. Risk of silicosis per unit CDE vs. CDE mid-point

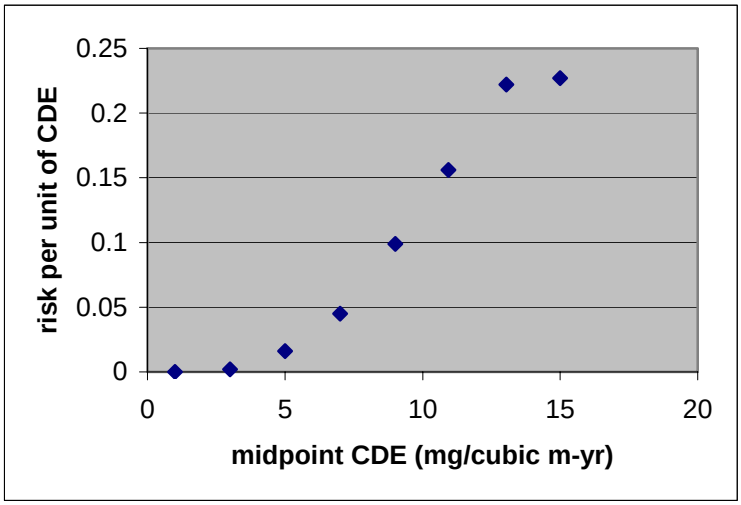
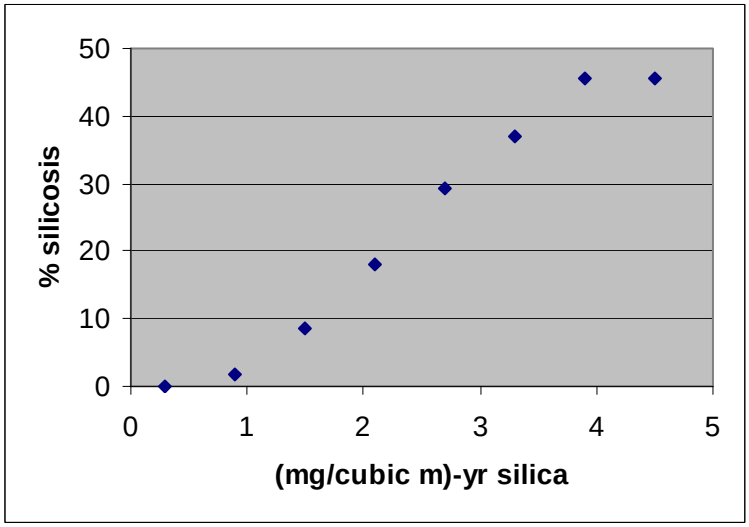


Figure 2. Percent silicosis among workers at each silica level



The estimate of 30% silica in the South African gold mine dust relied on estimates by Beadle (1971) for the period 1956-1960. Gibbs and Du Toit (2003) made a detailed review of the methodology used to estimate silica in those mines. They state that the exact relationship between respirable mass concentrations and theoretically derived concentrations cannot be determined. However, with many uncertainties, they estimate that the quartz percentage was more likely to be closer to 54%, than to 30%. The article also quotes a more recent analysis of quartz content of South African mining rock by Kielblock *et al*. (1997) that gives the overall silica content of the dust as being closer to 15% for the late 1980s to early 1990s, which would become 27% after applying the Gibbs and Du Toit correction factor of 1.8. Dr. Eva Hnizdo (personal communication, 2003), now with the U.S. National Institute of Occupational Safety

and Health (NIOSH), provided a summary of various other estimates that have been made. "Past surveys indicate that the amount of airborne respirable dust in SA gold mines in 1980's and in 1970's was on average around 0.4 mg/m^3 with average quartz concentration of 0.08 mg/m^3" (about 20%). She cited a Ph.D. thesis by R.E.G. Rendall, in which the silica percentage averaged 22% during the period from 1956 to 1972. Since Gibbs and Du Toit (2003) admitted that there were many uncertainties in their reevaluation, and since other estimates of percent silica were lower than the value of 30% used by Hnizdo and Sluis-Cremer (1993), OEHHA selected 30% silica as a reasonable estimate.

Hong Kong granite workers (Ng and Chan, 1994)

Ng and Chan (1994) investigated silicosis among 338 male workers, who had worked at least one year between 1967 and 1985 in two granite quarries in Hong Kong. Three readers examined the chest radiographs. Silicosis was defined as an ILO classification of at least 1/1 (for small rounded opacities) or greater, assigned by at least two of the three readers. Exposure was estimated for each worker based on job category and particle counts. Thirty-six workers (10.6%) were designated silicotic. Both a logistic and a linear model fit the data well. The study suffered because only about half of the previously employed granite workers were studied, which probably led to an underestimate of silicosis risk in at least the highest exposure category and maybe in others. The data are summarized in Table 7.

Table 7. Silica exposure and silicosis in Ng and Chan (Finkelstein, 2000)

Mean cumulative exposure (mg/m^3)-y	*Prevalence of silicosis* [a]
< 1	0%
3.1	13%
7.1	25%
22	22%

[a] rounded opacities determined by at least 2 of 3 readers (Table 3 of Ng and Chan)

Scottish coal workers (Miller *et al.,* 1998)

Miller *et al.* (1998) described the radiographic changes in 547 male Scottish coal workers exposed to unusually high concentrations (> 1 mg/m^3) of respirable quartz during the 1970s. Of the 1416 men who had worked at one colliery during that time, at least 200 were dead and another 156 could not be contacted. Of the remaining, 876 were asked to be in a health survey, and 711 agreed. Of these 551 were surveyed. Chest radiographs were taken. Classifications of the films under the ILO (1980) scheme were related by logistic regression to existing data on an individual's exposures to respirable dust and to quartz. From the median of the results of the three readers, 203 men (38%) showed progression of at least one profusion category on the ILO scale (for example from 2/1 to 2/2) from the various 1970s surveys to the follow up in 1990-1991. A total of 158 men (29%) had a profusion of at least 1/0, 103 (19%) had a profusion of at least 1/1, and 47 (8.6%) of at least 2/1 at the follow up survey. Large opacities were recorded as present by at least two readers for 14 (2.6%) of the men. Profusion of small opacities was firmly related to exposures in the 1970s; it was more strongly related with quartz than with the non-quartz fraction of the dust. Estimates of risk of silicosis by logistic regression over the range of quartz exposures are tabulated below in the Summary Table 13. The silica exposures of some

men at this mine were associated with considerable progression of X-ray abnormalities after exposure ended which illustrates the problems caused by incomplete follow-up. In addition only 39% (551/1416) of the original cohort was surveyed. Buchanan *et al*. (2003) determined quantitative relationships between silica exposure and silicosis in this cohort. They estimated that a miner exposed for 15 years to 100 μg/m^3 respirable quartz (1.5 mg/m^3-year) would have a risk of silicosis (in this case an ILO reading > 2/1) of 0.0248 fifteen years after exposure ended. Workers who also had several months exposure to high concentrations (2000 μg/m^3) would have much greater risk of silicosis. Note that the ILO cut-off criterion of 2/1 applied to this cohort is higher than in all the other studies.

Gold miners in South Dakota (Steenland and Brown, 1995)

Steenland and Brown (1995) studied a very large cohort (3330) of white male gold miners in South Dakota, who had worked at least 1 year underground between 1940 and 1965 (average = 9 years underground). The mine dust contained on average 13% silica (range = 1-48%). A job-exposure matrix was created for full-time underground workers grouped into five categories. The authors estimated that most miners were exposed to a median silica level of 0.05 mg/m^3, but that those hired before 1930 were exposed to a median level of 0.15 mg/m^3. A total of 170 cases of silicosis (5.1% of the cohort) was determined from death certificates only (n = 128 cases), from two cross-sectional radiographic surveys in 1960 and 1976 (n = 29 cases; ILO category 1/1 or greater), or from both (n = 13 cases). Unfortunately, only 25% of living cohort members were surveyed radiographically. The risk of silicosis was less than 1% with a cumulative exposure under 0.5 mg/m^3-years and increased to 68% to 84% for the highest cumulative exposure category (more than 4 (mg/m^3)-years) (Table 8).

Table 8. Risk of silicosis for cohort by cumulative exposure (Table 3, Steenland and Brown)

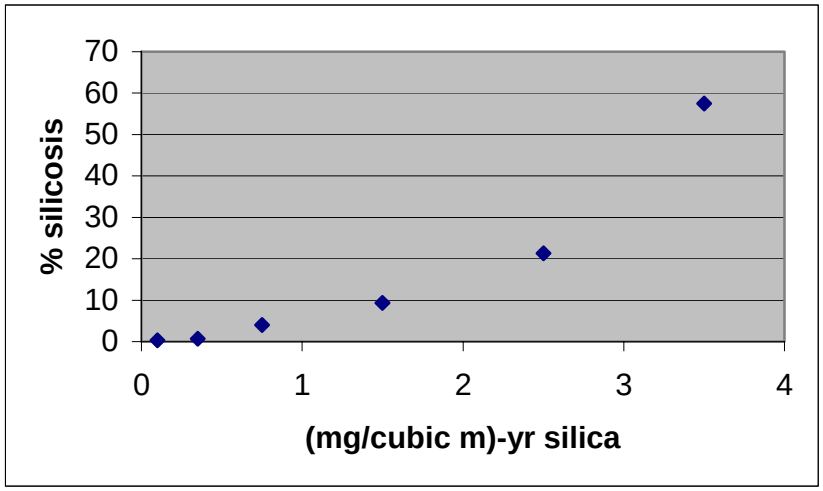
Silica exposure in (mg/m^3)-yrs: range (midpoint)	*Miners with silicosis*	*Number entering exposure category*	*Number at this exposure level*	*Cumulative[a] Risk*	*Mean years of exposure*	*Mean year first exposed*
0-0.2 (0.10)	5	3330	1530	0.002	2.9	1953
0.2-0.5 (0.35)	5	1800	740	0.005	9.7	1948
0.5-1.0 (0.75)	15	1060	376	0.017-0.022[b]	15.4	1942
1.0-2.0 (1.50)	33	684	353	0.060-0.084[b]	13.2	1931
2.0-3.0 (2.50)	44	331	206	0.167-0.245 [b]	18.8	1926
3.0-4.0 (3.50)	42	125	73	0.403-0.534[b]	25.5	1921
>4.0	26	52	52	0.678-0.844[b]	30.6	1914

[a] Cumulative risk = 1−exp[−sum of (hazards * interval width)], where the hazards for each category of cumulative exposure are:
no. cases/(width*(no. entering category – 0.5*no. cases – 0.5*no. withdrawals))
[b] Cumulative risk adjusted for age and calendar time (Steenland and Brown, 1995)

The best predictor of disease was cumulative exposure, followed by duration of exposure, and then by average exposure. Figure 1 of Steenland and Brown indicates that a plot of their data for silicosis risk versus cumulative silica exposure was similar to a plot of the data of Hnizdo and

Sluis-Cremer (1993). After adjustment for competing risks of death, Steenland and Brown estimate that a 45-year exposure to 90-100 μg/m^3 silica would lead to a lifetime risk of silicosis for gold miners of 35% to 47%. A limitation of this study is the reliance on death certificates rather than on ILO interpretation of radiographs. In addition no mention was made of validating the data on the death certificates. It was also not clear what, if any, autopsy data were available. A plot of silicosis incidence among the workers (as determined by OEHHA staff) actually exposed to the estimated level of silica is given in Figure 3 below.

Figure 3. % Silicosis vs. silica exposure in Steenland and Brown (see Table 8)



Miners in Leadville, Colorado (Kreiss and Zhen, 1996)

Kreiss and Zhen (1996) investigated the exposure-response relationships for silicosis among 134 male miners over 40 years old in Leadville, Colorado. The men had been studied three years earlier in a random sample of respiratory disease in their community (Kreiss *et al*., 1989). Of 100 dust-exposed miners, 32 had radiologic profusions of small opacities of ILO category 1/0 or greater at a mean of 36.1 years since their first silica exposure. Of miners with cumulative silica exposures of 2 (mg/m^3)-years or less, 20% had silicosis while 63% of miners accumulating greater than 2 (mg/m^3)-years had silicosis. Average silica exposure was also strongly associated with silicosis prevalence rates (Table 9).

Table 9. Miners studied by Kreiss and Zhen (1996)

Average silica exposure	*% silicotics*
0.025-0.05 mg/m^3	13% (5/38)
> 0.05-0.1 mg/m^3	34% (15/44)
> 0.1 mg/m^3	75% (9/12)
Cumulative silica exposure	*% silicotics*
≤ 2 (mg/m^3)-y	20% (14/70)
2 – 4 (mg/m^3)-y	63% (15/24)

Based on logistic regression models of the form $R(x) = [1 + \exp(-\alpha - B'x]^{-1}$, Kreiss and Zhen concluded that the risk of silicosis was best predicted by elapsed time since last silica exposure together with either (1) cumulative silica exposure or (2) a combination of average silica exposure and duration of exposure. Exposure-response relationships were substantially higher using measured silica exposures (compared to using estimated silica exposures based on measured total dust exposures and assuming a constant silica proportion of dust). The risk of silicosis in this study is higher than in workforce studies having no follow-up of those leaving the mining industry (e.g., Muir *et al*., 1989) and in studies without job title-specific silica measurements (e.g., Hnizdo and Sluis-Cremer, 1993). But the risk is comparable to several recent studies of exposure-response relationships for mining dust (e.g., Ng and Chan, 1994; Steenland and Brown, 1995) (see Summary Table 13 below). A limitation relative to other studies is the small number of subjects (100) in the group.

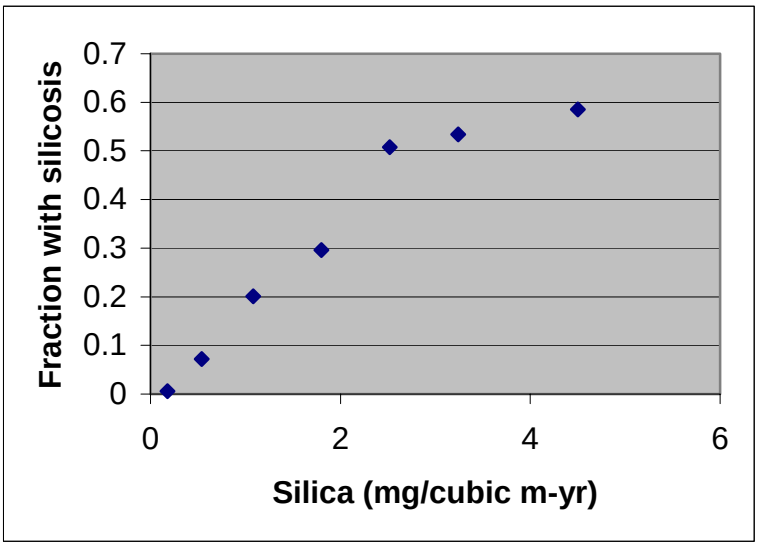
Chinese tin miners (Chen *et al*., 2001)

Chen *et al*. (2001) found a clear exposure-response relationship between silica dust exposure and silicosis in a cohort of 3010 (2795 male and 215 female) miners employed for at least 1 year during the period 1960-1965 in any of four Chinese tin mines. Each cohort member was followed through 1994. Historical Chinese total dust (CTD) data were used to create a job exposure matrix for each facility, job title, and calendar year. The CTD data were converted to estimates of respirable crystalline silica for comparison with findings from other epidemiological studies of silicosis (including some of those above). Each miner's work history was abstracted from employment records. The diagnosis of silicosis was based on 1986 Chinese Roentgen diagnostic criteria for pneumoconiosis. The criteria classified silicosis as stages I-III, similar to an ILO classification of 1/1 or greater. Of the 3010 miners, 1015 (33.7%) were identified as silicotic (mean age = 48.3 years, with a mean of 21.3 years after first exposure) (Table 10). Among the silicotics, 684 (67.4%) developed silicosis after their tin mine exposure had ended (mean = 3.7 years after). The risk of silicosis was strongly related to cumulative exposure to silica. The Weibull distribution gave a very good fit to the data. The risk of silicosis was less than 0.1% when CTD was less than 10 (mg/m^3)-yr (= 0.36 (mg/m^3)-yr of respirable crystalline silica). The risk of silicosis increased to 68.7% when CTD exposure was equal to 150 (mg/m^3)-yr (= 5.4 (mg/m^3)-yr of respirable crystalline silica). Latency period was not correlated to the risk of silicosis or to cumulative dose. From their data the authors predicted a 55% risk of silicosis for 45 years exposure to 0.1 mg/m^3 respirable crystalline silica, the workplace exposure limit (4.5-(mg/m^3)-years silica). Figure 4 plots the fraction of the workers in Chen *et al*. with silicosis (column 2 in Table 10 divided by column 4) exposed to a given level of silica (mid-point – in parentheses in column 1 of Table 10), as calculated by OEHHA staff.

Table 10. Cumulative silicosis risk based on cumulative total dust (CTD) (Table 5, Chen *et al*., 2001)

Range of CTD exposure in (mg/m^3)-y/ (silica mid-point)	*Cases of silicosis (n)*	*Workers entering category*	*Workers at this level of CTD/silica*	*Cumulative risk based on Weibull model*	*Mean net exposure (years)*	*Mean latency (years)*
<10 (0.18)	2	3010	333	0.001	2.2	14.7
10-19.99 (0.54)	24	2677	334	0.010	5.3	21.3
20-39.99 (1.08)	126	2343	626	0.070	9.3	22.0
40-59.99 (1.80)	127	1717	429	0.145	11.9	21.5
60-79.99 (2.52)	196	1288	386	0.285	9.9	20.3
80-99.99 (3.24)	141	902	264	0.405	10.8	19.0
100-149.99 (4.50)	244	638	417	0.663	13.1	20.4
≥ 150 (≥ 5.4)	155	221	221	0.917	15.7	25.4

Figure 4. Percent silicosis vs. silica level from Chen *et al*.



Industrial sand workers (McDonald *et al*., 2001; Hughes *et al*., 2001; Rando *et al*., 2001)

McDonald *et al*. (2001) studied a cohort of 2670 men employed before 1980 for 3 years or more and followed through 1994 in one of nine North American sand-producing plants and in a large associated office complex (since most of the office employees had previously worked in the mines). They found 37 deaths due to silicosis and silicotuberculosis. The mean exposure of the cohort was 42 $\mu g/m^3$ silica (Rando *et al*., 2001). Odds ratios for silicosis mortality, determined using conditional multiple logistic regression (SAS software), were significantly related to cumulative silica exposure (Hughes *et al*., 2001) (Table 11). The odds ratios are in general agreement with those in the gray foundry workers of Rosenman *et al*. (1996).

Table 11. Median cumulative silica exposure and odds ratio (Table 3 in Hughes *et al*., 2001)

	No lagging			*Lagged 15 yr*	
Median exposure in (mg/m^3)-y	*Silicotics (n)*	*Odds ratio*[a]	*Median exposure in (mg/m^3)-y*	*Silicotics (n)*	*Odds ratio* [a,b]
0.832	7	1.00	0.142	7	1.00
2.744	7	1.27	1.229	7	2.54
6.916	8	2.62	2.583	7	4.55
12.084	7	2.13	7.990	8	5.16

[a] Matched odds ratio relative to lowest cumulative exposure category. Although labeled a cohort study, the data analysis compared cases of silicosis with non-silicotic controls.
[b] Significant increasing trend across exposure categories (see Hughes *et al*. for more details)

Ceramic workers (Cavariani *et al*., 1995; Legrand-Cattan *et al*. (1998)

Cavariani *et al*. (1995) investigated the incidence of silicosis among 2,480 men in the ceramics industry in central Italy. The workers were surveyed during the period 1974-1987 and followed through 1991 with annual chest radiographs. The cumulative risk of silicosis (ILO category 1/1 or greater) was 48% after 30 years of employment. A multivariate Cox's proportional hazards model indicated that silicosis increased linearly up to the period of 25-29 years employment. A hazard risk of 14.6 was found comparing those with ≥ 30 years exposure to those employed 10 years. Smoking significantly contributed to the model, but its role was unclear.

Legrand-Cattan *et al*. (1998) examined the dose-response relationship in two French ceramic plants. A 1992 cross-sectional study included more than 200 silica-exposed workers. Three ILO certified B readers read chest radiographs. Silica was sampled in the airborne dust. The results are tabulated below (Table 12).

Table 12. Silicosis in two French ceramic plants (Legrand-Cattan *et al*., 1998)

Cumulative exposure to silica in (mg/m^3 – years)	*Number of workers at this level*	*Number with small opacities with ILO profusion ≥ 1/0*	*Percent*
< 0.35	50	2	4
0.35 – 1.08	57	8	14
1.09 – 1.77	55	11	20
> 1.77	55	17	31
Total	217	38	(18)

A dose response relationship is clear; the authors reported a p value of 0.002. However, the study is limited by the lack of follow-up of the workers.

Silica particle size

Data on silica particle size in the various workplaces are limited. Hnizdo and Sluis-Cremer (1993) stated that they studied respirable particles (range of 0.5 to 5 μm). According to Witschi

and Last (2001), silica particles with a diameter of 1 μm (range = 0.5 - 3 μm) appear to be the most fibrotic in humans. NIOSH (1974) reviewed the existing literature and found that in five diatomite plants the mean silica diameter was 1.1 μm (range = 0.5 - 2 μm). For nine potteries the particle size was 1.2 μm. For 18 foundries, more than 90% of the particles were less than 3 μm. The majority of particles to which shipyard sandblasters were exposed was also less than 3 μm. In the Vermont granite sheds, 10 mppcf (million particles per cubic foot) granite dust were initially estimated to be equal to 0.1 mg/m^3 respirable quartz. Steenland and Brown (1995) used this estimate for silica in South Dakota gold mines. Assuming that the density of quartz is 2.65 g/cm^3 and that the quartz particles are spherical, the data indicate that the particles have a diameter of 0.59 μm. NIOSH (1974) listed 0.94 μm as the median particle size in metal mines. No indication was given of the dispersion of the particle sizes around the average value. Davis *et al*. (1983) used the value of 10 mppcf in granite sheds as equal to 0.075 mg/m^3 silica. For that estimation OEHHA staff calculated the particle diameter to be 0.53 μm. Thus, existing data indicate that the majority of silica in the workplace is respirable.

Risk estimation for silicosis from epidemiologic studies

The data from the above studies have been used by a number of investigators (Finkelstein, 2000; Chen *et al*., 2001; Hughes, 1995) and by OEHHA staff to estimate percent silicosis based on cumulative silica exposure in units of mg/m^3-yr. The results are summarized in the following table (Table 13):

Table 13. Summary - Estimates of % silicosis based on cumulative silica exposure in (mg/m^3)-y

Study	*Population (number with silicosis)*	*Exposure of 2 (mg/m^3)-y*	*Exposure of 4 (mg/m^3)-y*	*Exposure of 4.5 (mg/m^3)-y*
Muir *et al*., 1989	2109 male Ontario hard rock miners ("15")	0.4[a,c]	1.2[a,c]	2[b]
Rosenman *et al*., 1996	1072 Midwestern foundry workers (28)	2[a]	10[a]	3[b]
Graham *et al*., 1991	408 Vermont granite workers (35)	~3[c]	—	—
Hughes *et al*., 1998	1809 white male diatomaceous earth workers (81)	1.1 (low intensity) 3.7 (high intens.)[a]	4 (low) 12 (high)[a]	—
Park *et al*., 2002	2342 white male diatomaceous earth workers (80)	~7[e]	13[e]	14[e]
Hnizdo & Sluis-Cremer 1993	2235 white male South African gold miners (313)	5[a] 10[c]	52[a] 60[c]	77[b]
Ng & Chan, 1994	338 male Hong Kong granite workers (36)	6[a]	15[a]	15-20[b]
Miller *et al*., 1998	547 Scottish coal miners (103[f] or 158[f])	6[a]	30[a]	—
Steenland & Brown, 1995	3330 male S. Dakota gold miners (170)	8[a]	53[a]	70[b]
Kreiss & Zhen, 1996	100 miners in Leadville, CO (32)	11[a]	53[a]	92[b]
Chen *et al*., 2001	3010 Chinese tin miners (1015)	14[d]	47[d]	55[b]

[a] From Table II of Finkelstein (2000)
[b] From Table 6 of Chen *et al*. (2001)
[c] From Tables 3 and 4 of Hughes (1995)
[d] Interpolated by OEHHA staff from Fig. 2 of Chen *et al*. (2001).
[e] Estimated by OEHHA staff from Table 4 of Park *et al*. (2002)[f] 158 had an ILO reading ≥ 1/0, while 103 had an ILO reading ≥ 1/1.

In Table 13, a total of 17,300 workers was studied; 1908 (11%) were classified as silicotic. The 11% is likely an underestimate of the incidence of silicosis due to lack of follow-up by chest radiographs during life in some cohorts and to the lack of an autopsy after death.

Determination of LOAEL and NOAEL for silicosis (Rice and Stayner, 1995)

In another approach to the data, Rice and Stayner (1995) identified the NOAEL and LOAEL for silicosis in several studies (Table 14). The study of Hnizdo and Sluis-Cremer (1993) yielded both a LOAEL and a NOAEL.

Table 14. Estimates of NOAELs and LOAELs for silicosis (Rice and Stayner, 1995)

Study	*Subjects*	*NOAEL in μg/m³*	*LOAEL in μg/m³*
Davis *et al*., 1983	969 granite workers	67.5	
Hnizdo and Sluis-Cremer, 1993	2235 gold miners	7	20
McDonald and Oakes, 1984	1321 gold miners	-	8[a]
"	64 gypsum miners	35	49
Muir *et al*., 1989	2109 gold miners	Could not determine	Could not determine
Rice *et al*., 1986	888 dusty trade workers	80-100	200-252

[a]McDonald and Oakes (1984) considered this value to be only an approximation.

Proposals to change the occupational exposure limit

Silicosis is still being diagnosed at death in workers who were supposed to be exposed to occupational levels of 50-100 μg/m^3. Thus there have been recommendations that the occupational exposure limit for respirable, crystalline silica (specifically alpha-quartz) be lowered from the current level of 100 μg/m^3 to 50 μg/m^3 (NIOSH, 1974; Rosenman *et al*., 1996; ACGIH, 1999; Finkelstein, 2000). In 2000 the ACGIH lowered its TLV for quartz from 100 to 50 μg/m^3. In 1986, WHO recommended that the level be set at 40 μg/m^3 (WHO, 1986). Greaves (2000) recommended that the TLV be lowered to 10 μg/m^3. Based on existing data Greaves (2000) estimated that at 10 μg/m^3 the incidence rate for ILO grade 1/0 silicosis would be less than 5%, while for grade 1/1 it would be less than 2%. Chen *et al*. (2001) recommended that the TLV be lowered to 5 μg/m^3. "If the lifetime risk of silicosis is to be under 1 in 1000 (a criterion used by OSHA) for a lifetime exposure of 45 years, then the mean Chinese total dust concentration must be lower than 0.14 mg/m^3 (or lower than 0.005 mg/m^3 respirable crystalline silica)" (Chen *et al*., 2001). Mannetje *et al*. (2002) pooled data from six occupational cohorts. These included four groups discussed above: diatomaceous earth workers, Vermont granite workers, U.S. industrial sand workers, and South Dakota gold miners. Among them 170 deaths from silicosis were reported. The estimated mortality risk from silicosis to age 65 after 45 years of exposure at 100 μg/m^3 silica was 13 per 1000, while the risk of death at 50 μg/m^3 was estimated at 6 per 1000. Both estimates are above the 1 per 1000 risk acceptable to OSHA. Mannetje *et al*. also concluded that the occupational standards for silica should be lowered, but they did not specify a level. They further state that their estimates of silicosis mortality are probably underestimates due to exposure misclassification and to outcome misclassification, since deaths due to silicosis might have been coded to tuberculosis or chronic obstructive pulmonary disease.

C. Silica exposure and lung cancer

In 1997 IARC classified respirable crystalline silica in Class 1, a Known Human Carcinogen, based on occupational epidemiologic studies. However, chronic RELs are not based on cancer endpoints. Further, there is no approved cancer potency factor for silica.

V. Effects of Animal Exposures

Several papers have reported that freshly fractured quartz, which has increased surface activity, causes greater inflammation than "aged" quartz. Vallyathan *et al*. (1991) reported that "fresh" silica was 4.2-fold more potent than silica aged for 1-2 days in decreasing the membrane integrity of male rat macrophages; 50% more potent in activating hydrogen peroxide secretion by macrophages; and 4.6-fold more potent in stimulating cellular chemiluminescence. Vallyathan *et al*. (1995) reported that inhalation of 19.3 mg/m^3 aged (for 2 months) quartz for five hours/day for 10 days by male Fischer 344 rats increased the number of cells recoverable by bronchoalveolar lavage (BAL) (Table 15). Aged quartz also gave histopathologic evidence of increased pulmonary infiltrates, showed higher levels of biochemical markers of lung injury, increased lipid peroxidation, and increased the ability of pulmonary phagocytes to produce more oxygen radicals than air-exposed controls. These pulmonary responses were significantly more pronounced after inhalation of 22.4 mg/m^3 freshly fractured quartz.

Table 15. Cells recovered in bronchoalveolar lavage from rats (Vallyathan *et al*., 1995)

Cell type	*Room Air*	*Aged quartz*	*Freshly fractured*	*Fresh/aged*
Total cells	7.1±0.78*	9.3±1.2	20.4±2.2	2.2
Macrophages	6.7±0.69	4.7±0.79	5.4±0.78	1.1
Neutrophils	≥ 0.038	5.3±0.66	10.4±1.44	2.0
Lymphocytes	≥ 0.038	1.7±0.25	3.6±0.27	2.1
Red blood cells	≥ 0.038	1.7±0.26	6.0±0.57	3.5

* Cell counts are in millions. Each value is the mean ± standard error of 5 rats.

Burns *et al.* (1980) exposed female Balb/c mice for up to 39 weeks to 4.9 mg/m^3 Min-U-Sil brand crystalline silica. By 24 weeks silica-laden macrophages were present in the lungs. After 39 weeks of exposure, silicotic lesions were seen in the lungs and adjacent lymph nodes (Table 16).

Davis *et al*. (1998) exposed mice to an aerosol of cristobalite silica (mass median aerodynamic diameter (MMAD) = 1.7 μm) for five hours/day in order to examine (1) the effects of exposure dose, (2) the evolution of disease over time, and (3) the variation in responses among strains. In C3H/HeN mice, incremental, cumulative exposure doses of cristobalite (10 mg/m^3 for 8 days, 43 mg/m^3 for 9 days, and 70 mg/m^3 for 12 days) caused (1) increased initial lung dust burden at 12 to 16 weeks post-exposure, (2) progressively intense pathological responses, and (3) increased total lung collagen (as measured by hydroxyproline).

The histopathological changes and total lung collagen increased with time after exposure. Silicosis was compared in four inbred strains of mice (BALB/c, C3H/HeN, MRL/MpJ, New

Zealand Black) 16 weeks after aerosol inhalation exposure to cristobalite (70 mg/m^3, 5 hours/day, 12 days). C3H/HeN mice had histopathological silicotic lesions, enlarged intrapulmonary lymphoid tissue, and increased lung wet weight, increased bronchoalveolar lavage (BAL) recoverable macrophages, lymphocytes, and neutrophils, and increased total lung collagen (hydroxyproline analyses). BALB/c mice developed slight pulmonary lesions. MRL/MpJ mice showed prominent pulmonary infiltrates with lymphocytes. New Zealand Black (NZB) mice developed extensive alveolar proteinaceous deposits, inflammation, and fibrosis. The authors found both dose-time-response relationships and a substantial variation of responses among mouse strains to the high level, short duration exposure.

At Brookhaven National Laboratory, groups of Fischer 344 rats were exposed to 0, 2, 10, and 20 mg/m^3 Min-U-Sil brand silica (alpha-quartz) for six months (Kutzman, 1984a; as summarized by USEPA, 1996). Other groups of rats had the same exposure but were allowed to "recover" in air for an additional 6 months (Kutzman, 1984b; as summarized by USEPA, 1996). Significant alterations in total lung weight, total lung collagen, total elastin per unit lung dry weight, and total protein per unit lung dry weight at 2 mg/m^3 silica and microscopic evidence of silicotic lesions at the higher silica levels indicated that 2 mg/m^3 was a LOAEL for silica effects. After six months in clean air the silica-induced lesions appeared to worsen.

Muhle *et al*. (1989) exposed groups of 50 male and 50 female rats to 1 mg/m^3 DQ12 quartz six hours/day, five days/week for 24 months. DQ12 contains 87% crystalline alpha-quartz, has a mass median aerodynamic diameter (MMAD) of 1.3 μm, and is 74% respirable. Moderate fibrosis was seen in 85 animals, slight fibrosis in 13, and very slight fibrosis in 1 (total rats with fibrosis = 99/100). Varying amounts of peribronchial granulomatous foci were noted in 95 rats.

Muhle *et al*. (1998) reported lung fibrosis in hamsters exposed to 3 mg/m^3 DQ12 silica. After 18 months of exposure to DQ12 for 6 h/day, 5 days/week, all hamsters in the group of 15-19 animals necropsied had very slight fibrosis. Approximately 100 silica-exposed animals were exposed for five more months to air only. Afterward 22.2% had very slight fibrosis, 68.7 % had slight fibrosis, and 1% had moderate fibrosis (i.e., more than 90/100 hamsters had lung fibrosis). No collagen measurements were reported. Thus, rats, mice, and hamsters show pulmonary fibrosis after crystalline silica exposure at and above 1 mg/m^3.

Wagner *et al*. (1968) exposed dogs up to 2.5 years, guinea pigs up to 18 months, and rats up to 2 years for 6 hours/day, 5 days/week to 61% cristobalite (in calcined diatomaceous earth). Dust exposures were 2 and 5 million particles per cubic foot (mppcf), equivalent to 0.2 and 0.5 mg/m^3 cristobalite (USEPA, 1996), with occasional excursions to 50 mppcf. No lung fibrosis was detected at these levels but all levels caused accumulation of inflammatory cells in the lung parenchyma. However, in dogs fibrotic nodules developed in the hilar lymph nodes with more nodules at 5 mppcf than at 2 mppcf.

Scheuchenzuber *et al*. (1985) examined immunologic responses in Balb/c mice following inhalation of 1.954 mg/m^3 silica for 150, 300, or 570 days. Mice exposed for 570 days were tested immediately post-exposure. Those exposed for 150 or 300 days were tested immediately or were rested for 30 or 150 days to allow for possible recovery from effects of dust inhalation. Silica inhalation suppressed the number of specific plaque-forming cells (PFC) in the spleen produced in response to aerosolized *E. coli*. After 570 days of inhalation, silica also reduced the

ability of alveolar macrophages to phagocytize *Staphylococcus aureus in vitro* and impaired the ability to lyse allogeneic tumor cells (from mice other than Balb/c) *in vitro*. Silica inhalation did not affect antibody-dependent cell-mediated cytotoxic and mitogenic responses by splenic lymphocytes. (Fibrosis was not an endpoint measured, but the effect level is similar to the LOAELs in other animal studies.)

Table 16. Animal studies of silica inhalation analyzed by USEPA (1996)

Study	*Species*	*Duration*[a]	*LOAEL*
Muhle *et al*., 1989	Rat	24 mo	1.0 mg/m^3
Scheuchenzuber *et al*., 1985	Mice	150-570 d	2.0
Burns *et al*., 1980	Mice	3-39 wk	4.9
Kutzman, 1984a	Rat	6 mo	2.0
Kutzman, 1984b	Rat	6 mo + 6 mo recovery	2.0
Wagner *et al*., 1986	Dog	Up to 2.5 yr	0.2

[a] Inhalation exposure was generally for 6 h/day, 5 d/wk.

Quartz has the ability to induce the generation of free radicals and to cause oxidative stress in tissues. Many substances that affect the quartz surface can modify this ability. Some of these modifiers could originate from other minerals, which exist together with quartz in nature. Donaldson and Borm (1998) proposed that the hazard posed by quartz may vary widely depending on the origin of the silica sample or on its contact with other chemicals/minerals. Such mechanistic data could assist in the interpretation of epidemiological studies such as those above. Experimentally their group found that DQ12 quartz, a European quartz standard which is often used in experimental studies of silica effects, is much more inflammatory in rat lung than respirable silica collected from two workplaces (Clouter *et al*., 2001).

Humans appear to show adverse effects of silica exposure at lower levels than animals (compare LOAELs in Table 16 to LOAELs/NOAELs in Table 14). Rodents tend to be obligate nose-breathers and to have extensive nasal turbinates, which may result in less silica reaching the lower lung. For silica, results in animals may not be a good predictor of human effect levels.

VI. Derivation of Chronic Reference Exposure Level (REL)

Key study	Hnizdo and Sluis-Cremer, 1993
Study population	2235 white South African gold miners
Exposure method	Workplace inhalation
Critical effects	Silicosis (313 miners) (14 %)
LOAEL	3 mg/m^3-years CDE (9 miners with silicosis)
NOAEL	2 mg/m^3-years CDE (0 miners with silicosis) or 600 $\mu g/m^3$-years silica (dust = 30% silica)
BMC_{01}	2.12 (mg/m^3)–yr CDE or 0.636 (mg/m^3)–yr silica
Exposure continuity	8 h/day, 5 d/wk
Exposure duration	Average of 24 years dust exposure (9-39 years)
Average experimental exposure	210 $\mu g/m^3$-yr silica at BMC_{01} (636 x 10 m^3/20 m^3 x 5 d/7 d x 48 wk/52 wk) 210 $\mu g/m^3$-yr/24 yr = 8.75 $\mu g/m^3$
Human Equivalent Concentration (HEC)	8.75 $\mu g/m^3$
LOAEL uncertainty factor	Not needed in BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Inhalation Reference Exposure Level	3 $\mu g/m^3$ (based on 30% silica in mine dust)

First supportive study	Steenland and Brown, 1995
Study population	3330 S. Dakota gold miners
Exposure method	Workplace inhalation
Critical effects	Silicosis (170 miners) (5.1%)
LOAEL	0-0.2 mg/m^3-years (5 miners with silicosis)
NOAEL	Not found
BMC_{01}	0.34 (mg/m^3)–yr (see text below)
Exposure continuity	8 h/day, 5 d/wk
Exposure duration	3-36 years (average 9 years underground)
Average experimental exposure	112 $\mu g/m^3$-y (340 x 10 m^3/20 m^3 x 5 d/7 d x 48 wk/52 wk) 112 $\mu g/m^3$-y/9 y = 12.4 $\mu g/m^3$
Human Equivalent Concentration (HEC)	12.4 $\mu g/m^3$
LOAEL uncertainty factor	Not needed in BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Inhalation Reference Exposure Level	4 $\mu g/m^3$

Second supportive study	Hughes *et al*., 1998
Study population	1809 California diatomaceous earth workers
Exposure method	Workplace inhalation
Critical effects	Silicosis (81 workers) (4.5%)
LOAEL	> 1, ≤ 3 mg/m^3-years (17 workers with silicosis)
NOAEL	≤ 1 mg/m^3-years (6 cases). (Six cases were observed, but the paper's authors assigned the group a Relative Risk = 1 for silicosis.)
Exposure continuity	8 h/day, 5 d/wk
Exposure duration	1-45 years (mean = 11.5 years)
Average experimental exposure	≤ 330 μg/m^3-y (1000 x 10/20 x 5/7 x 48/52) ≤ 330 μg/m^3-y/ 11.5years = ≤ 29 μg/m^3
Human Equivalent Concentration (HEC)	29 μg/m^3
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Inhalation Reference Exposure Level	10 μg/m^3 (based on authors' NOAEL) 3 μg/m^3 (if authors' NOAEL is really a LOAEL)

Third supportive study	Chen *et al*. (2001)
Study population	3010 Chinese tin miners
Exposure method	Workplace inhalation
Critical effects	Silicosis (1015 workers) (33.7 %)
LOAEL	10-19.99 mg CTD/m^3-years (24 cases)
NOAEL	≤ 10 mg CTD/m^3-years (2 cases) ≤ 360 μg silica/m^3 - years
BMC_{01}	132 μg silica/m^3 - years
Exposure continuity	8 h/day, 5 d/wk
Exposure duration	2.2 years for NOAEL group
Average experimental exposure	40 μg/m^3-y (132 x 10/20 x 5/7 x 48/52) 40 μg/m^3-y/2.2 years = 18 μg/m^3
Human Equivalent Concentration (HEC)	18 μg/m^3
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Inhalation Reference Exposure Level	6 μg/m^3

The large study of 2235 white South African gold miners by Hnizdo and Sluis-Cremer (1993) not only determined a NOAEL of 2 (mg/m^3)-yr CDE (600 μg/m^3-yr silica), but also had sufficient dose-response data for a BMC derivation. This study was powerful enough to detect a 1.9% incidence of silicosis (9 cases out of 474 exposed) at 0.9 mg/m^3-yr silica (0/204 vs. 9/474,

$\chi^2 = 3.94$, $p < 0.05$). Because this incidence represents approximately the sensitivity limit of the data, and silicosis is a severe irreversible endpoint, the BMC_{01} (*i.e.,* the lower bound estimate of the concentration at which 1% of the population develops silicosis) was selected as the basis of the chronic REL. In benchmark analysis of chronic animal studies, BMC_{05} is typically regarded by OEHHA as equivalent to a NOAEL. However, the power of this large-scale study is sufficient to demonstrate measurable responses below the 5% incidence level (which cannot then be logically considered a no-effect level). Furthermore, the endpoint measured in this epidemiological study is considered to be severe, since it represents the occurrence of clinically recognizable and irreversible disease, rather than an adverse physiological or biochemical response or a histopathological result seen at autopsy.

Benchmark Concentration (BMC) models, developed by the USEPA (BMDS versions 1.3, 1.3.1, and 1.3.2), were fit to the human data in Hnizdo and Sluis-Cremer (1993) (Table 6 and Figure 2 above). Fitting the probit model to the log dose of the Hnizdo and Sluis-Cremer (1993) data yielded an MLE_{01} of 2.45 (mg/m^3)–yr CDE and a BMC_{01} of 2.12 (mg/m^3)–yr CDE ($\chi^2 = 0.64$; p value for fit = 0.9957) (Figure 5, Table 17). (For comparison the BMC_{05} was 3.73 (mg/m^3)–yr CDE.) Fitting the logistic model to the same data yielded a BMC_{01} of 1.73 (mg/m^3)–yr CDE ($\chi^2 = 2.71$; p value for fit = 0.8446) (Table 17). The BMC_{01} from these data is about the same as the apparent NOAEL. In general, a BMC is preferred to a NOAEL because the BMC takes into account all the dose response data in a study. The apparent NOAEL may be either above or below an actual effect level, depending on the study design and distribution of the data.

Figure 5. Probit model fit to the log dose of the Hnizdo and Sluis-Cremer data.

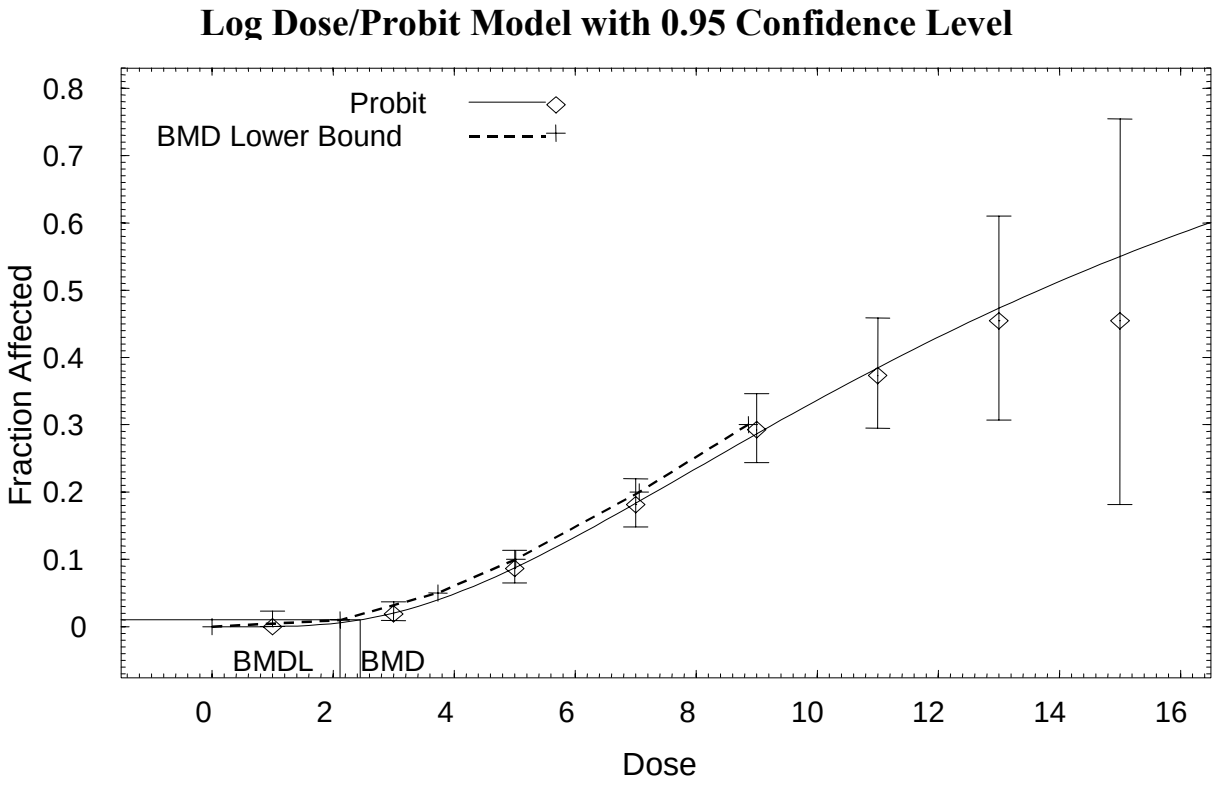


Table 17. Fits of benchmark models to the Hnizdo and Sluis-Cremer (1993) data

BMDS Model	*MLE_{01}*	*BMC_{01}*	*p value for fit*
Probit-log-dose	2.45 (mg/m^3)–yr CDE	2.12 (mg/m^3)–yr CDE	0.9957
Logistic-log-dose	2.07	1.73	0.8446
Multistage (n=2)	2.47	1.89	0.7213
Quantal-quadratic	1.62	1.54	0.5017
Probit	1.56	1.32	0.0079
Logistic	1.48	1.28	0.0003
Quantal-linear	0.37	0.34	0.0000

In the first supportive study Steenland and Brown (1995) found five cases of silicosis in the lowest dose group of 0 – 0.2 (mg/m^3)-yr and considered the group to be a LOAEL (Table 8 above). None of the BMDS models gave an acceptable fit at the $p \geq 0.05$ level using six or seven silica levels. The closest was the quantal quadratic model ($\chi^2 = 9.62$; $p = 0.0473$), which resulted in a BMC_{01} for silica of 0.43 (mg/m^3)–yr using the six lowest levels of silica. In risk assessment, the highest dose or doses are often dropped in order to obtain an acceptable fit of the model to the data. This is reasonable with the benchmark approach since the highest doses should be least informative and the doses in the low dose region near the benchmark should be most informative (USEPA, 1995; Filipsson *et al*., 2003). Fitting the probit model to the log dose of the five lowest silica levels from Steenland and Brown yielded a BMC_{01} of 0.34 (mg/m^3)–yr CDE ($\chi^2 = 1.32$; p value for fit = 0.5177). [For comparison, $BMC_{05} = 0.85$ (mg/m^3)–yr CDE.] Fitting the quantal quadratic model gave a BMC_{01} of 0.45 (mg/m^3)–yr ($\chi^2 = 3.36$; $p = 0.3395$). Use of the BMC_{01} value of 0.34 (mg/m^3)–yr CDE from the probit model resulted in a chronic REL estimate for crystalline silica of 4 $\mu g/m^3$. Steenland and Brown stated that "silicosis has no background rate for non-exposed populations that changes with age or calendar time" and thus they assumed that the five silicotics in the 0 – 0.2 (mg/m^3)-yr were exposed to silica in the mines.

In a second supportive study, Hughes *et al*. (1998) found six cases of silicosis in the lowest exposure group of ≤ 1 mg/m^3-yr but considered that group to be a NOAEL, not a LOAEL. A chronic REL of 10 $\mu g/m^3$ was calculated from the data. Hughes *et al*. (1998) cite examples of possible non-occupational chest radiograph opacities (due for example to age or smoking) to explain the six cases in the lowest exposure group. However, due to the rarity of silicosis the six cases are biologically significant. OEHHA considers that the six cases may be work related, not cases of environmental or background silicosis. When a LOAEL to NOAEL UF of 3 is applied to the data of Hughes *et al*. (1998), the estimated REL is 3 $\mu g/m^3$.

In a third supportive study, Chen *et al*. (2001) found two cases of silicosis in the lowest exposure group of ≤ 10 mg CTD/m^3-years and considered that exposure level to be a NOAEL. One of the advantages of the benchmark dose analysis is that a NOAEL/LOAEL controversy, such as the one above with the Hughes *et al*. (1998) data, does not impact the procedure. The chart of the

Chen *et al*. data above (Figure 4) indicates that the dose response is linear at low doses. Fitting the probit model to the log dose of the four lowest data points yielded a BMC_{01} of 0.132 (mg/m^3) - yr CDE ($\chi^2 = 2.19$; p value for fit = 0.335). Use of five, six, or seven data points gave BMC_{01}s of 0.14 to 0.17, but the p values were less than 0.1. For comparison, fitting the logistic model to the log dose of the four lowest data points yielded a BMC_{01} of 0.093 (mg/m^3) - yr CDE ($\chi^2 = 4.86$; p value for fit = 0.0879). An inhalation chronic Reference Exposure Level for crystalline silica of 6 $\mu g/m^3$ was estimated from the Chen *et al*. data.

Other investigators have approached the possibility that some opacities on radiographs may be due to background influences. Based on reading 1422 films of unexposed blue-collar workers, Castellan *et al*. (1985) stated that the use of the median result of 3 readers (the same number used by Hughes *et al*.) rarely results in interpreting a chest radiograph as ILO category $\geq$ 1/0 in workers who were not exposed to dust (and regardless of smoking status). A literature analysis by Meyer *et al*. (1997) used ILO 1/0 as a basis of classification and found a background level of opacities in populations thought to be free of dust exposure. In North America, the incidence was 0.6% (6/1000) in people under 50 years of age and 2.3% (23/1000) in those over 50. Thus the six cases (6/1452) in the lowest exposure group of Hughes *et al*. (1998) might not be work-related.

The USEPA (1996) did a benchmark analysis with the Hnizdo and Sluis-Cremer (1993) data. They estimated that the lower bound for a 1% risk for silicosis (BMC_{01}) was 1.31 (mg/m^3)-yr, which by their methods is equivalent to a continuous, 70-year exposure to 6.7 $\mu g/m^3$ silica. However, USEPA did not do a formal Reference Concentration (RfC) derivation for silica by either the BMC/UF or NOAEL/UF approach.

The key (Hnizdo and Sluis-Cremer, 1993) and supporting (Steenland and Brown, 1995; Hughes *et al*., 1998; Chen *et al*., 2001) studies were of human adults, nearly all males, who were presumably healthy, at least initially, since they were able to work. Thus there is need to protect the sensitive members of the population, especially children, in whose airways deposition of silica particles will be greater (Phalen *et al*., 1985; Schiller-Scotland *et al*., 1994; Oldham *et al*., 1997; Bennett and Zeman, 1998). In addition women may be more sensitive than men to the development of silicosis (Gerhardsson and Ahlmark, 1985; Katsnelson *et al*., 1986). The selection of three as the intraspecies uncertainty factor (UF_H) was based on several considerations.

(1) The workers who developed silicosis at low silica concentrations are by definition the most sensitive workers to silica-induced silicosis. Because of the large population of workers examined in these studies (17,300), the sensitive individuals represent at least part of the range of sensitivity to be expected in the general population. This may justify reducing the UF_H from the default value of 10. On the other hand, since these workers did not include children, the elderly, or females (except for the 215 females in Chen *et al*.), some uncertainty related to inter-individual variability remains. Therefore, a UF_H of 3 rather than 1 is chosen.

(2) Mukherji *et al*. (1993) reported mean ambient silica levels in California (see the Appendix to this report). At Santa Maria (an urban site) the level was 2.3 $\mu g/m^3$; in Santa Ynez, CA (a rural site) 0.6 $\mu g/m^3$; and in Buellton, CA (a remote background site) 0.2

$\mu g/m^3$ of crystalline silica. Thus, use of a human intraspecies uncertainty factor (UF_H) of 10 with the data from the key study would result in an estimated chronic REL of 0.9 $\mu g/m^3$, a level in the range of ambient levels in California. Although the reported levels at the urban site may (according to the authors) have reflected some anthropogenic contributions such as disturbance and tracking of siliceous road dust, the rural and remote site values are apparently (perhaps conservatively) reflective of the natural background to which all California residents are exposed. (U.S. EPA (1996) found slightly higher average ambient levels, but this average may include some sites affected by disturbance and emissions.) There is no evidence that these background levels of silica are causing silicosis. On the other hand, silicosis in the general population is not a target for medical attention, and autopsy rates are very low, so the possibility of a low frequency of response at these levels cannot be entirely dismissed. On balance, it appears plausible that a REL of 3 $\mu g/m^3$ (benchmark + $UF_H = 3$) would be protective of the general population. (The REL of 3 $\mu g/m^3$ is based on 30% silica in the mine dust.)

(3) The dose-response curve for silicosis due to inhalation of crystalline silica is steep, and an upward curvature of this dose response was seen in some studies (Figure 7-1 in USEPA, 1996). It is notable that, whereas exposures in the 1-3 $\mu g/m^3$ range are apparently without effect (based on the benchmark calculations and the California ambient background data), Rice and Stayner (1995) described a LOAEL for silicosis of 8 $\mu g/m^3$ in gold miners (Table 14; based on data from McDonald and Oakes [1984]). This finding may partly reflect differences in physical state of the silica, and co-exposures, but it implies that, although the chronic REL should be protective of public health, exposures only moderately exceeding the REL may lead to clinically observable disease.

The animal studies gave LOAELs for silica of 0.2 mg/m^3 in dogs and from 1 to 4.9 mg/m^3 in rodents. After extrapolation to equivalent continuous time and application of LOAEL to NOAEL, interspecies, and intraspecies UFs, the estimated chronic RELs from animal data are all less than 1 $\mu g/m^3$. This reflects in part the greater uncertainty in extrapolating from animal studies to predicted human health effects.

The silica particles of concern in the causation of silicosis are those of respirable size. California EPA defines 'respirable' as particles 10 μm or less MMAD. Consistent with this definition, a size criterion of 10 μm or less MMAD is recommended for use with the chronic REL derived above. This also reflects the usual type of sampler (for "PM_{10}") used for ambient air sampling in the general environment. The NIOSH-specified personal samplers used in many occupational studies have not been validated for the combination of sensitivity, sampling duration, and operating conditions required for environmental measurements.

There are differences in the size range distribution between a typical PM_{10} measuring device and the NIOSH type personal samplers, or similar static devices, used by the investigators in the epidemiological studies. These samplers capture particles in a size range where the MMAD is 4 μm or less. (This is a mean cutoff size; in other words at this size the pass-through efficiency is 50%. In fact, a substantial proportion of larger particles between 4 and 10 μm in aerodynamic diameter will be collected.) Clearly, the level of confidence in the use of the Reference Exposure

Level is greatest for materials where the included range of particle sizes (and reactivity) is similar to those seen in the occupational studies.

The NIOSH samplers are designed to mimic the size range of particles that reach into the bronchiolar and alveolar spaces (what the occupational community calls respirable). PM_{10} samplers are meant to capture particles that deposit along the entire respiratory tree, including those that deposit in the tracheobronchial and alveolar regions. Deposition by particle size is complex, and is dependent on the aerodynamic diameter, hygroscopicity, and electrostatic charge of the particles, and on a number of host factors including airway structure and geometry, as well as depth, rate, and mode of breathing (nasal vs. oronasal). The fractional deposition in the various regions of the respiratory tract is not linear with respect to size. Generally, though, larger particles impact higher in the respiratory tree (the extrathoracic and tracheobronchial regions), while smaller particles show greater deposition in the lower tracheobronchial and alveolar regions. There are a number of models of regional deposition in the respiratory tract as well as some measurements. Chan and Lippmann (1980) showed peak alveolar deposition for particles about 3 μm MMAD with deposition dropping above and below that. Their data and model indicate tracheobronchial deposition rises rapidly above about 3 μm MMAD. Available data also indicate significant inter-individual variability in fractional deposition. The ICRP (1994) model used in evaluating risk from radioactive particles indicates that total deposition in the respiratory tract for particles 3 μm in activity median thermodynamic diameter (AMTD) is about 0.78 with a regional deposition fraction of 0.077 for the alveolar region for a reference male worker during nasal breathing. The same model predicts a total deposition in the respiratory tract of 0.77 for 10 μm AMTD particles and a deposition fraction of 0.024 in the alveolar region. Thus, many particles with a 10 μm MMAD get into the alveolar space. A smaller difference in regional deposition is predicted for mouth breathers. Therefore, if only the size range measured by the samplers used in the studies were considered, the measurement might underestimate the amount of silica that is deposited in the gas exchange regions of the lung, depending on the actual particle size distributions in the occupational studies and in the environments in which the REL is to be applied. Unfortunately, neither the occupational nor the environmental silica particle size distributions are known; measurements have been reported only in terms of PM_4 or PM_{10} cutoff values.

It is frequently assumed that the silicosis is induced by that fraction of the silica that reaches the alveoli. Nevertheless, no actual data exonerate the coarser particles in the 4 - 10 μm range. Such particles clearly can enter the bronchioles and alveoli. As noted above, there is a difference in the size range of the particles measured by the samplers used in the epidemiological studies, and in those captured by a PM_{10} sampler. However, we do not believe that applying the chronic REL to silica captured in a PM_{10} sampler (or to models based on emission inventories developed with that criterion) will result in a gross overestimation of the hazard index from industrial sources of silica.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for silica include:

(1) The availability of several long-term studies of inhalation in workers at varying exposure concentrations (see Summary Table 13 above), with adequate histopathological and radiologic analysis, and with adequate follow-up.
(2) The finding of a dose-response effect for silicosis in several of the studies (e.g., Hnizdo and Sluis-Cremer, 1993; Steenland and Brown, 1995; Chen *et al*., 2001).
(3) The observation of a NOAEL in some studies including the key study (summarized by Rice and Stayner, 1995).
(4) The power of the Hnizdo and Sluis-Cremer (1993) data to detect a small effect.

Major areas of uncertainty are:

(1) The limited follow-up of the cohort members in some studies (e.g., Muir *et al*., 1989; Rosenman *et al*., 1996) with consequent under-ascertainment of silicosis (even to the extent that such studies are useless for determining exposure-response).
(2) The general underestimation of silicosis by radiography alone (Hnizdo *et al*., 1993).
(3) The possible underreporting of silicosis where complete radiographic data and autopsy data are not available (Steenland and Brown, 1995).
(4) The uncertainties in exposure estimation, especially when reconstructing historical levels of silica exposure (Seixas *et al*., 1997; Gibbs and Du Toit, 2002) including the variability in the estimates of percent quartz in the South African mine dust (Beadle, 1971; Hnizdo and Sluis-Cremer, 1993; Kielblock *et al*., 1997; Gibbs and Du Toit, 2002; Hnizdo, personal communication)
(5) The differences in percent silicosis in different studies at what were considered similar silica levels and similar exposure duration (see Summary Table 13 above).
(6) The variability in toxicity of various forms of silica (e.g., freshly fractured vs. aged quartz; cristobalite vs. quartz) although all forms have toxicity (Table 15).
(7) The limited information on silica particle size (including its variability) in the epidemiological studies, other than that the silica was respirable, and the variability in particle deposition as a function of particle size in the respiratory tract in the human population (e.g., Heyder *et al*., 1982; ICRP, 1994; Hattis *et al*., 2001).
(8) The use of area samplers rather than personal samplers to estimate exposure.

VIII. Potential for Differential Impacts on Children's Health

Silica is a respiratory irritant. Respiratory irritants often have steep dose-response curves. Thus use of the human intraspecies uncertainty factor (UF_H) of 3 should result in a REL that adequately protects children. Exacerbation of asthma, which has a more severe impact on children than on adults, is a known response to some respiratory irritants. However, there is no direct published evidence to quantify such a response to silica, or to quantify a differential effect of silica on infants or children. The epidemiological studies used in the derivation of the REL did not include children. If children's susceptibility were much greater than that of adults, it would be expected that clinical disease would be evident in children following exposures in the

upper range of the respirable silica levels measured in ambient air in California. No such reports have been identified in the literature.

OEHHA is currently evaluating its risk assessment methodology, in particular the UF_H, for its adequacy in protecting infants and children. Since children have smaller airways than adults and breathe more air on a body weight basis, deposition of particles in the airways in children is likely greater than that in adults exposed to the same concentration (Phalen *et al*., 1985; Schiller-Scotland *et al*., 1994; Oldham *et al*., 1997; Bennett and Zeman, 1998).

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X. Appendix

Particulate Levels of Interest for Exposure to Respirable Crystalline Silica Isomorphs

150 $\mu g/m^3$	Federal 24 hour PM_{10} standard (particulate matter < 10 μm diameter)
65 $\mu g/m^3$	Federal 24 hour $PM_{2.5}$ standard (PM < 2.5 μm in diameter)
50 $\mu g/m^3$	California 24 hour PM_{10} standard
50 $\mu g/m^3$	Federal PM_{10} annual standard (chronic exposure)
50 $\mu g/m^3$	8 hour TLV for quartz, cristobalite, and tridymite for workers
50 $\mu g/m^3$	estimated workplace LOAEL for silicosis from studies by Theriault *et al*.
20 $\mu g/m^3$	CA annual PM_{10} standard (chronic exposure) (arithmetic mean)
15 $\mu g/m^3$	Federal annual $PM_{2.5}$ standard (chronic exposure)
12 $\mu g/m^3$	CA annual $PM_{2.5}$ standard (chronic exposure) (arithmetic mean)
12 $\mu g/m^3$	current silica TLV adjusted to equivalent continuous exposure (50 $\mu g/m^3$ x 8 h/24 h x 5 d/7d)
10 $\mu g/m^3$	TLV for silica proposed by Greaves (2000)
8 $\mu g/m^3$	current silica TLV further adjusted by 46/70 years occupational exposure
8 $\mu g/m^3$	estimated high-end ambient crystalline silica level in US (USEPA, 1996)
6.7 $\mu g/m^3$	lower bound on 1% risk of silicosis estimated by USEPA (1996)
5 $\mu g/m^3$	TLV for silica proposed by Chen *et al*. (2001)
5 $\mu g/m^3$	"acceptable" ambient level for silica (10% of PM_{10}) (USEPA, 1996)
5 $\mu g/m^3$	RfC for diesel exhaust particulate, a respirable PM
3 $\mu g/m^3$	estimated average ambient exposure to crystalline silica (USEPA, 1996)
3 $\mu g/m^3$	draft silica chronic REL proposed by OEHHA
2.3 $\mu g/m^3$ (1.17-3.46; n=12)*	silica level during 1989 in Santa Maria, CA (urban site)
0.6 $\mu g/m^3$ (0-1.44; n=16)*	silica level during 1989 in Santa Ynez, CA (rural site)
0.2 $\mu g/m^3$ (0-1.15; n=18)*	silica level during 1989 in Buellton, CA (remote background)

* mean, range, and number of crystalline silica measurements (Mukherji *et al*., 1993)